REMARKS

Applicants have amended claims 14, 15, 17, and 18, and added new claims 24-27. Applicants have further cancelled non-elected claims 1-13, 16, and 19-23. No new matter has been introduced by the amendment. In particular, support for amended claims 14, 15, 17, and 18 can be found, e.g., at page 10, lines 24-25 and page 1, line 29 through page 2, line 1 of the specification. Support for newly added claims 24-27 can be found, e.g., at page 1, lines 21-24 and page 9, line 6 through page 13, line 13 of the specification.

Claims 14, 15, 17, 18, and 24-27 are now pending. Reconsideration of the application, as amended, is requested in view of the following remarks:

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 14, 15, 17, and 18 as being indefinite. Specifically, the Examiner asserted that the term "*Pseudomonas*" recited in these claims fails to point out which species of *Pseudomonas* it represents. The Examiner further asserted that the phrase "a receptor binding domain of a *Pseudomonas* exotoxin A" recited in these claims is vague and confusing because it conveys that there are more than one receptor binding domains and more than one exotoxin A. See the Office Action, pages 2-3, part 7.

Pursuant to the Examiner's suggestion, Applicants have replaced the phrase "a receptor binding domain" recited in claims 14, 15, 17, and 18 with "the receptor binding domain."

Applicants would like to point out that all species of the *Pseudomonas* family produce exotoxin A, and that the term "*Pseudomonas*" recited in claims 14, 15, 17, and 18 represents any species of the *Pseudomonas* family. Similarly, the phrase "a *Pseudomonas* exotoxin A" refers to an exotoxin A produced by any species of the *Pseudomonas* family.

For the amendments and reasons set forth above, Applicants submit that claims 14, 15, 17, and 18 particularly point out and distinctly claim the subject invention, and the Examiner's rejection should be withdrawn.

Rejection under 35 U.S.C. § 102

I

The Examiner rejected claims 14 and 18 under 35 U.S.C. § 102(e) as being anticipated by Lorberboum-Galski et al. (U.S. Patent No. 6,140,066; "'066"). See the Office Action, pages 3-4, part 9.

Claim 14 is directed to a nucleic acid encoding a polypeptide that contains (1) the receptor binding domain of a *Pseudomonas* exotoxin A and (2) at least two copies of a peptide sequence. Claim 18 is directed to a nucleic acid similar to that of claim 14 except that copies of the peptide sequence are in a consecutive series.

As correctly pointed out by the Examiner, '066 discloses a DNA sequence encoding a polypeptide comprising a full-length *Pseudomonas* exotoxin A and **two** copies of a linker sequence in a consecutive series. The Examiner rejected claims 14 and 18 as being anticipated by '066, contending that the full-length *Pseudomonas* exotoxin A inherently contains the receptor binding domain.

Applicants have amended claims 14 and 18 so that they are now drawn to a nucleic acid encoding a polypeptide containing at least **three** copies of an antigenic peptide sequence, thereby overcoming the Examiner's rejection.

II

The Examiner rejected claims 14, 15, and 18 under 35 U.S.C. § 102(b) as being anticipated by Hickey et al. (WO 97/15325; "'325"). See the Office Action, page 4, part 10.

Claims 14 and 18 have been discussed in section (I) above. Claim 15 is drawn to a nucleic acid similar to that of claim 14 except that the peptide sequence contains SEQ ID NO:1.

As correctly pointed out by the Examiner, '325 teaches a recombinant DNA encoding a hybrid protein that contains a *Pseudomonas* exotoxin A and **two tandem copies** of GnRH (SEQ ID NO:1). The Examiner concluded that claims 14, 15, and 18 are anticipated by '325.

As mentioned above, Applicants have amended claims 14 and 18 so that they are now drawn to a nucleic acid encoding a polypeptide containing at least **three** copies of an antigenic peptide sequence. Claim 15 has been amended likewise. Therefore, the Examiner's rejection has been overcome.

III

The Examiner rejected claims 14, 17, and 18 under 35 U.S.C. § 102(b) as being anticipated by Hwang et al. (Cell (1987) 48:129-136; "Hwang-1987") or Hwang et al. (J. Biol. Chem. (1989) 264:2379-2384; "Hwang-1989"). See the Office Action, pages 4-5, part 11.

Claims 14 and 18 have been discussed in section (I) above. Claim 17 is drawn to a nucleic acid similar to that of claim 14 except that the polypeptide contains 10-20 copies of the peptide sequence.

As correctly pointed out by the Examiner, Hwang-1987 teaches a recombinant nucleic acid encoding a mutant *Pseudomonas* exotoxin A that includes the receptor binding domain, and Hwang-1989 teaches an expression plasmid encoding a *Pseudomonas* exotoxin A that includes the receptor binding domain. It is the Examiner's position that the term "peptide sequence," as recited in claims 14, 17, and 18, encompasses both antigenic and non-antigenic sequences. It is also the Examiner's position that, as claims 14, 17 and 18 do not specifically recite the length of the peptide sequence, even a single amino acid residue constitutes a peptide sequence. The Examiner concluded that claims 14, 15, and 18 are anticipated by Hwang-1987 or Hwang-1989, as both of them disclose a nucleic acid encoding a polypeptide that contains the receptor binding domain and at least two or ten discontinuous copies of a peptide sequence of a single amino acid residue or at least two consecutive copies of a peptide sequence of a single amino acid residue.

Applicants would like to point out that the length of the peptide sequence recited in claims 14, 17, and 18 is defined in the specification as follows:

> "The peptide sequence must be at least two amino acids in length (e.g., at least 3, 5, 7, 9, or 10 amino acids in length). In a preferred embodiment, the peptide sequence can be less than 1000 amino acids in length (e.g., less than 500, 100, 50, or 20 amino acids in length)." See page 1, lines 25-29 of the specification.

The specification further describes the nature of the peptide sequence:

> "The peptide sequence can include any antigen in which an immune response against it is beneficial, such as gonadotropin releasing hormone or GnRH (e.g., EHWSYGLRPG [SEQ ID NO:1]) or a fragment of a vaccinia virus coat protein (e.g., LIGICVAVTVAI [SEQ ID NO:2]). See page 1, line 29 through page 2, line 1 of the specification.

In any event, Applicants have amended claims 14, 17, and 18 so that they are now drawn to a nucleic acid encoding a polypeptide containing **at least three copies of an antigenic peptide sequence**. Note that a single amino acid residue does not constitute an antigenic peptide sequence). As neither Hwang-1987 nor Hwang-1989 teaches a nucleic acid encoding a polypeptide that contains the receptor binding domain of *Pseudomonas* extoxin A and at least three copies of an antigenic peptide sequence, they do not participate amended claims 14, 17, and 18. Therefore, the Examiner's rejection has been overcome.

For the amendments and reasons set forth above, Applicants submit that claims 14, 15, 17, and 18 are not participated by the prior art references cited by the Examiner, and rejection should be withdrawn.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected claims 14, 15, 17, and 18 as being unpatentable over Potter et al. (WO 96/24675; "'675") or Russell-Jones et al. (WO 91/02799; "'799") in view of Hwang-1989 and Pastan et al. (U.S. Patent No. 4,892,827; "827"). See the Office Action, pages 5-7, part 13. Applicants respectfully traverse.

As mentioned above, amended claims 14, 15, 17, and 18 are directed to nucleic acids encoding polypeptides containing the receptor binding domain of *Pseudomonas* exotoxin A (PE) and at least three copies of GnRH.

'675 and '799 teach a nucleic acid encoding a polypeptide that contains multiple copies of GnRH and a carrier peptide (**a bacterial leukotoxin** in '675 and **a TraTp sequence** in '799). Hwang-1989, on the other hand, teaches that the receptor binding domain of PE can be used for vaccination against PE-mediated cytotoxicity. '827 teaches modified *Pseudomonas* exotoxins including hybrid proteins containing modified *Pseudomonas* exotoxins and luteinizing hormones.

It is the Examiner's position that it would have been prima facie obvious to a skilled artisan to replace leukotoxin in '675 or TraTp in '799 with the receptor binding domain of PE described in Hwang-1989 or '827. The Examiner asserted that a skilled artisan would have been motivated, with a reasonable expectation of success, to produce the claimed nucleic acid

encoding a polypeptide that contains the receptor binding domain of PE and multiple copies of GnRH, as GnRH is a luteinizing hormone.

Applicants would like to point out that none of the references cited by the Examiner, alone or in combination, provides motivation for a skilled artisan to combine these references. Specifically, there is no indication in either '675 or '799 that the receptor binding domain of PE can serve as a carrier. Hwang-1989 only teaches that the receptor domain of PE itself can be used for producing vaccines against PE-mediated cytotoxicity, but does not suggest that it can be used as an antigen carrier to facilitate induction of immune responses against the antigen. Further, the "modified *Pseudomonas* exotoxins" disclosed in '827 specifically refer to PE mutants containing "**deletions in at least domain 1A**" (the receptor binding domain). See, e.g., Abstract, cover page of '827. As such, '827 not only does not provide motivation for a skilled artisan to produce a nucleic acid encoding a polypeptide that contains the receptor binding domain of PE and multiple copies of GnRH, but also teaches away from the claimed nucleic acid.

For the reasons set forth above, '675 or '799, in combination with Hwang-1989 and '827, would not have motivated a skilled artisan to combine these references and derive at the claimed nucleic acid. In other words, claims 14, 15, 17, and 18 are patentably distinguishable over the cited art.

The Examiner also made of record but did not rely on two additional prior art references: Meloen et al. (Vaccine (1994) 12:741-746) and Chen et al. (Appl. Microbio. Biotechnol. (1999) 52:524-533). Applicants have reviewed them and found that they do not render claims 14, 15, 17, and 18 obvious.

CONCLUSION

Applicants submit that the grounds for rejection asserted by the Examiner have been overcome, and that claims 14, 15, 17, 18, and 24-27 as pending, define subject matter that is definite, novel, and nonbovious over the prior art. On this basis, it is submitted that allowance of this application is proper, and early favorable action is solicited.

Attached is a marked-up version of the changes being made by the current amendment.

Enclosed is a $460 check for the Petition for a Three-Month Extension of Time fee. Please apply any other charges to Deposit Account No. 06-1050, referencing Attorney Docket No. 08919-022001.

Respectfully submitted,

Date: 12-5-02

Y. Rocky Tsao

Y. Rocky Tsao, Ph.D., J.D.
Attorney for Applicants
Reg. No. 34,053

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

20550241.doc

Version with markings to show changes made

In the claims:

Claims 1-13, 16, and 19-23 have been cancelled without prejudice.

Claims 14, 15, 17, and 18 have been amended as follows:

14. (Twice Amended) A nucleic acid encoding a polypeptide, wherein the polypeptide comprises (1) [a] the receptor binding domain of a *Pseudomonas* exotoxin A, and (2) at least [two] three copies of [a] an antigenic peptide sequence.

15. (Twice Amended) A nucleic acid encoding a polypeptide, wherein the polypeptide comprises (1) [a] the receptor binding domain of a *Pseudomonas* exotoxin A, and (2) at least [two] three copies of [a] an antigenic peptide sequence comprising SEQ ID NO:1.

17. (Twice Amended) A nucleic acid encoding a polypeptide, wherein the polypeptide comprises (1) [a] the receptor binding domain of a *Pseudomonas* exotoxin A, and (2) 10 to 20 copies of [a] an antigenic peptide sequence.

18. (Twice Amended) A nucleic acid encoding a polypeptide, wherein the polypeptide comprises (1) [a] the receptor binding domain of a *Pseudomonas* exotoxin A, and (2) at least [two] three copies of [a] an antigenic peptide sequence in a consecutive series.